Bronchoscopic lung-volume reduction with Exhale airway stents for emphysema (EASE trial): randomised, sham-controlled, multicentre trial

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Summary

Background **Airway bypass is a bronchoscopic lung-volume reduction procedure for emphysema whereby transbronchial passages into the lung are created to release trapped air, supported with paclitaxel-coated stents to ease the mechanics of breathing. The aim of the EASE (Exhale airway stents for emphysema) trial was to evaluate safety and efficacy of airway bypass in people with severe homogeneous emphysema.**

Methods **We undertook a randomised, double-blind, sham-controlled study in 38 specialist respiratory centres worldwide. We recruited 315 patients who had severe hyperinflation (ratio of residual volume [RV] to total lung capacity of ≥0·65). By computer using a random number generator, we randomly allocated participants (in a 2:1 ratio) to either airway bypass (n=208) or sham control (107). We divided investigators into team A (masked), who completed pre-procedure and post-procedure assessments, and team B (unmasked), who only did bronchoscopies without further interaction with patients. Participants were followed up for 12 months. The 6-month co-primary efficacy endpoint required 12% or greater improvement in forced vital capacity (FVC) and 1 point or greater decrease in the modified Medical Research Council dyspnoea score from baseline. The composite primary safety endpoint incorporated five severe adverse events. We did Bayesian analysis to show the posterior probability that airway bypass was superior to sham control (success threshold, 0·965). Analysis was by intention to treat. This study is registered with ClinicalTrials.gov, number NCT00391612.**

Findings **All recruited patients were included in the analysis. At 6 months, no difference between treatment arms was noted with respect to the co-primary efficacy endpoint (30 of 208 for airway bypass *vs* 12 of 107 for sham control; posterior probability 0·749, below the Bayesian success threshold of 0·965). The 6-month composite primary safety endpoint was 14·4% (30 of 208) for airway bypass versus 11·2% (12 of 107) for sham control (judged non-inferior, with a posterior probability of 1·00 [Bayesian success threshold >0·95]).**

Interpretation **Although our findings showed safety and transient improvements, no sustainable benefit was recorded with airway bypass in patients with severe homogeneous emphysema.**

Funding **Broncus Technologies.**

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*See end of report for details of the EASE trial study group

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Introduction

Surgery to reduce lung volume in patients with pulmonary emphysema can increase residual volume (RV) and improve breathing mechanics and dyspnoea, even in individuals with homogeneous disease. However, with substantial surgical morbidity, adoption of this procedure has been low.[1–3]

Airway bypass is a bronchoscopic procedure to reduce lung volume that is designed for treatment of severe homogeneous emphysema. With this technique, passages are created in the bronchial airways to deflate air trapped in the emphysematous regions, and paclitaxel-eluting stents are placed to maintain passageway patency.[4,5] In preclinical, ex-vivo, and pretransplant studies, airway bypass released trapped air by bronchoscopic creation of transbronchial passageways.[5–8] In a feasibility study,[5] efficacy was shown for airway bypass at 6 months in patients with a ratio of RV to total lung capacity (TLC) of more than 67%, a proportion that is also predictive of improvement in forced vital capacity (FVC) after lung-volume reduction surgery.[9]

The Exhale drug-eluting stent (Broncus Technologies, Mountain View, CA, USA) is composed of stainless steel and silicone and contains paclitaxel, which is intended to inhibit fibrotic responses.[7] We designed the Exhale airway stents for emphysema (EASE) trial to investigate safety and efficacy of airway bypass for patients with severe homogeneous emphysema.

Methods

Participants

We undertook a multicentre, double-blind, randomised, sham-controlled trial at 38 specialist respiratory centres worldwide. The adaptive study design of the EASE trial and screening process to select patients with severe homogeneous disease has been published previously.[10]

Panel 1 summarises key inclusion and exclusion criteria. We focused inclusion criteria on definition of a

Panel 1: **Key inclusion and exclusion criteria**

Inclusion criteria

- Smoking history ≥20 pack-years
- ≥16 sessions of pulmonary rehabilitation over 6–10 weeks
- RV/TLC ≥0·65, RV >180% predicted
- FEV_1/FVC <70%
- FEV_1 ≤50% of predicted or FEV_1 <1 L
- Striking dyspnoea (≥2 on modified Medical Research Council scale)
- DL_{CO} ≥15% of predicted
- PaO_2 ≥45 mm Hg
- Homogeneous emphysema verified by CT core laboratory[10]

Exclusion criteria

- Body-mass index greater than 31·1 for men or 32·3 for women
- Change in FEV_1 (pre-bronchodilator to post-bronchodilator) >20%, or >200 mL if FEV_1 <1 L
- Pulmonary hypertension
- Arterial blood pH <7·35 or $PaCO_2$ >60 mm Hg
- Uncontrolled hypertension (systolic >200 mm Hg or diastolic >110 mm Hg)
- Clinically significant bronchiectasis
- Three or more respiratory infections requiring admission in the past 12 months, or respiratory infection <30 days before randomisation

RV=residual volume. TLC=total lung capacity. FEV_1=forced expiratory volume in 1 s. FVC=forced vital capacity. DL_{CO}=diffusing capacity of the lung for carbon monoxide. PaO_2=partial pressure of oxygen. $PaCO_2$=partial pressure of carbon dioxide.

	Masked	Unmasked
Subject-level	Participant Participant's family Participant's personal doctor or caregivers	None
Site-level	Team A (all post-procedure assessments) PFT technicians Exercise technicians	Team B (bronchoscopy team) Procedure room hospital personnel Radiologists
Sponsor-level	Executive management Trial database manager Internal statisticians All other staff except those specified	Safety director: aggregate data Personnel maintaining investigational devices: aggregate data External statisticians Study monitors: site-specific data only Procedural case support: site-specific data only

PFT=pulmonary function test.

Table 1: **Masking scheme**

population with severe hyperinflation. All participants had to undergo at least 6 weeks of pulmonary rehabilitation pre-procedure. Pulmonary rehabilitation entailed at least 16 sessions of instruction on individualised exercise, respiratory care, diaphragmatic breathing, nutrition, and group education to obtain the highest level of independent function. We measured pulmonary function tests with Crapo[11] normal values and did these tests according to guidelines of the American Thoracic Society and the European Respiratory Society.[12]

All study participants gave their written informed consent. Every centre's ethics committee approved the trial protocol. An independent data safety and monitoring board monitored the progress of the study, including maintenance of the double blind. Independent adjudicators reviewed adverse events according to a prespecified charter.

Randomisation and masking

On confirmation of study eligibility, we allocated participants randomly in a 2:1 ratio to either airway bypass or sham control using an independent, automated, internet-based service (Advance Research Associates, Mountain View, CA, USA), with a permuted block size of six and sequential assignment, stratified by investigational site.

To maintain the study blind, investigators were divided into team A (masked), which completed pre-procedure and post-procedure assessments, and team B (unmasked), which only did bronchoscopies without further interaction with patients. We communicated randomisation assignments to members of team B only. Participants were unaware of their assigned study arm for the first year of the trial. We informed them of their randomisation assignment at month 12. At every follow-up visit (day 1 post procedure and months 1, 3, 6, and 12), participants and personnel from team A completed questionnaires to assess maintenance of the double blind; all instances of unmasking were reported to the study sponsor. Table 1 presents the masking scheme.

Procedures

We did airway bypass and sham control (the index procedure) under general anaesthesia 1 day after randomisation took place. For airway bypass, we created passages and placed up to six stents (maximum of two stents per lobe, excluding the right middle lobe) per individual. Pre-procedure assessment of CT images by team A allowed for planning of stent placement, although team B decided on the final number of stents and their location during the procedure, according to local conditions and safety. We did the sham control in a similar manner to airway bypass, except no passages were created and no stents were placed. Post procedure, pulmonary rehabilitation of at least ten sessions was needed for 8 weeks or longer.

Study endpoints

The co-primary responder efficacy endpoint was met if the participant's FVC increased by at least 12% and their modified Medical Research Council dyspnoea score (mMRC; table 2) fell by 1 point from baseline at the 6-month follow-up visit. The primary safety composite endpoint was met with any of the following serious adverse events: major haemoptysis (≥200 mL estimated blood loss or requiring transfusion, or needing arterial embolisation or surgical or endoscopic intervention);

	Description
0	"I only get breathless with strenuous exercise"
1	"I get short of breath when hurrying on the level or walking up a slight hill"
2	"I walk slower than people of the same age on the level because of breathlessness or have to stop for breath when walking at my own pace on the level"
3	"I stop for breath after walking about 100 yards or after a few minutes on the level"
4	"I am too breathless to leave the house" or "I am breathless when dressing"

Table 2: **Modified Medical Research Council dyspnoea score**

respiratory failure needing ventilation for more than 24 h; pulmonary infection or exacerbation of chronic obstructive pulmonary disease (COPD) needing admission for longer than 7 days; pneumothorax for longer than 7 days, needing drainage; or death within 30 days of procedure or initial admission (if longer than 30 days), or death from respiratory causes.

Prespecified secondary efficacy endpoints included pulmonary function tests: measurements for RV, TLC, RV/TLC, FVC, and forced expiratory volume in 1 s (FEV_1); St George's respiratory questionnaire (SGRQ); 6-min walk test; and endurance cycle ergometry, set to 75% of maximum workload. We have described performance of these tests previously.[10] We did post-hoc analyses to assess endpoint outcomes at day 1 and months 1, 3, and 12.

CT methods

We calculated lung volumes (RV and TLC) from standardised CT chest images.[13] We assessed homogeneity with a modified National Emphysema Treatment Trial definition.[10] We derived the emphysema score per lobe by converting the proportion of pixels less than –910 Hounsfield units into a Likert scale, whereby homogeneity needed fewer than 2-unit differences between adjacent lobes.[14] A minimum total score of 8 was needed for entry into the trial. For measurement of lung volumes in voxels, we used a validated three-dimensional technique to guide automated lobar segmentation, as described previously on thick-section CT images, and then we tabulated by lobe, stents per patient, and stents per lobe. To assess stent patency, we did binary classification of every stent with at least two views. We defined "lumen completely clear" as an internal lumen that is visualised completely and is clear of CT density, whereas "not completely clear" included visualisation of CT density above that of air that occluded (partly or completely) the lumen.

Statistical analysis

We used a Bayesian adaptive approach to sample size, with interim looks scheduled at 225, 270, 315, 360, 405, and 450 participants. Bayesian statistics is an axiomatic

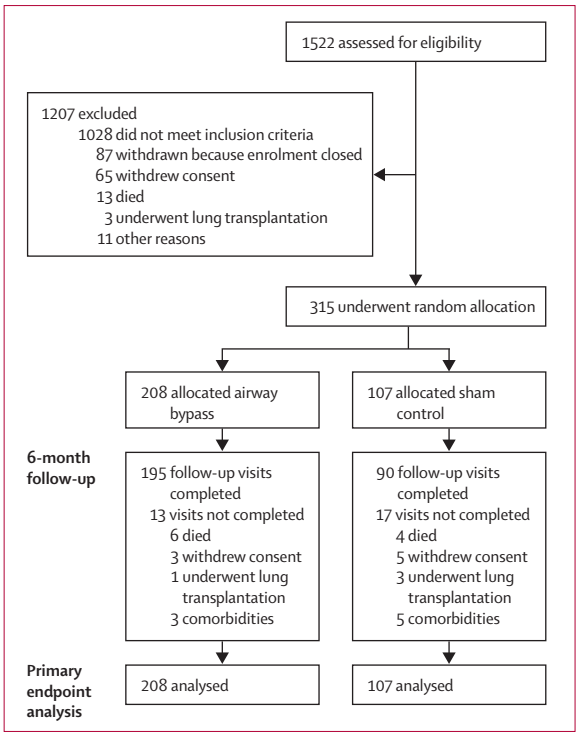

Figure 1: **Trial profile**

	Airway bypass (n=208)	Sham control (n=107)
Age (years)	64·1 (7·29)	65·2 (7·16)
Men	105 (50%)	56 (52%)
White ethnic origin	208 (100%)	104 (97%)
Smoking history (pack-years)	57·65 (28·82)	56·67 (27·11)
BMI (kg/m²)	23·27 (3·97)	23·61 (3·69)
BODE index	5·96 (1·26)	5·93 (1·2)
FEV_1 (L)	0·65 (0·19)	0·66 (0·21)
FEV_1 (% predicted)	23·23 (6·08)	23·55 (7·22)
FVC (L)	2·30 (0·68)	2·22 (0·60)
RV (L)	5·25 (1·16)	5·40 (1·24)
RV (% predicted)	244·14 (52·81)	248·46 (51·35)
TLC (L)	7·64 (1·56)	7·70 (1·54)
RV/TLC ratio	0·69 (0·06)	0·70 (0·06)
DL_{CO} (% predicted)	30·59 (11·45)	28·39 (10·44)
mMRC (0–4)	2·64 (0·62)	2·65 (0·57)
SGRQ (0–100)	56·6 (12·9)	58·04 (13·25)
Endurance cycle ergometry (s)	320 (235)	318 (220)
6-min walk test (m)	302 (88)	297 (85)

Data are number of patients (%) or mean (SD). BMI=body-mass index. BODE=BMI, airway Obstruction (measured by FEV_1), Dyspnoea (measured by mMRC), and Exercise tolerance (measured by 6-minute walk test). DL_{CO}=diffusing capacity of the lung for carbon monoxide. FEV_1=forced expiratory volume in 1 s. FVC=forced vital capacity. mMRC=modified Medical Research Council dyspnoea scale. RV=residual volume. SGRQ=St George's respiratory questionnaire. TLC=total lung capacity.

Table 3: **Baseline demographic, pulmonary, and functional characteristics**

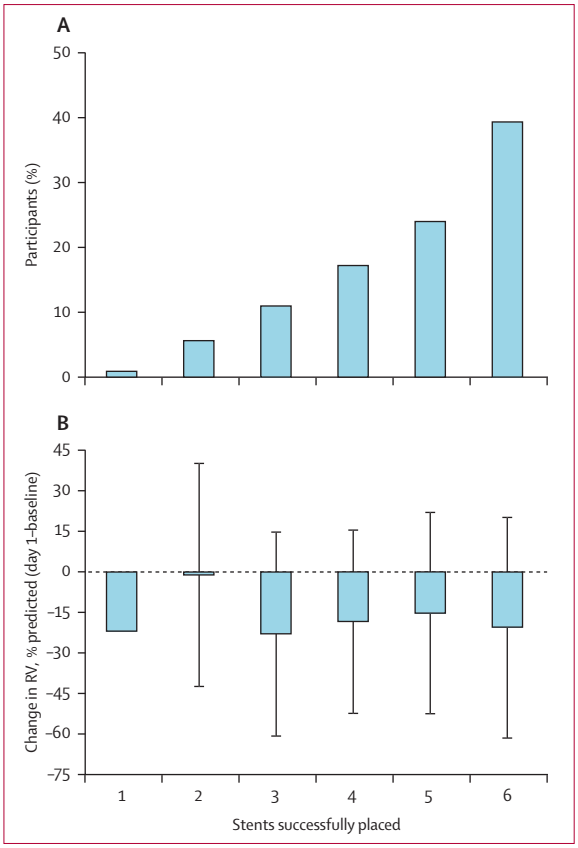

Figure 2: **Stent distribution (A) and change in percent predicted RV (B)**
Error bars in (B) represent SD. RV=residual volume.

	Airway bypass (n=208)	Sham control (n=107)
Participants having a composite safety event	30 (14·4%)	12 (11·2%)
Respiratory failure requiring mechanical ventilation for 24 h or longer	4 (1·9%)	0 (0%)
Pneumothorax requiring intercostal tube drainage for more than 7 days	2 (1·0%)	0 (0%)
Major haemoptysis	1 (0·5%)	0 (0%)
COPD or infection needing admission for longer than 7 days	22 (10·6%)	9 (8·4%)
Death at 30 days or earlier and respiratory death after 30 days	4 (1·9%)	4 (3·7%)

Data are number (%). Three patients assigned airway bypass and one allocated sham had several events. COPD=chronic obstructive pulmonary disease.

Table 4: **Composite primary safety endpoint, 6 months post procedure**

	Airway bypass (n=208)	Sham control (n=107)
Pneumothorax	3 (1·4%)	1 (0·9%)
Haemoptysis	1 (0·5%)	0 (0%)
COPD exacerbation or infection†	33 (15·9%)	9 (8·4%)
Non-respiratory death at 30 days or later	0 (0%)	0 (0%)

Data are number (%). COPD=chronic obstructive pulmonary disease. *Events meeting the definition of a primary safety composite endpoint are excluded. †Number reporting at least one COPD exacerbation or infection.

Table 5: **Respiratory serious adverse events, at 6 months post procedure***

approach that provides the probability of hypotheses conditional on observed data, compared with the traditional approach of calculating the probability of data conditional on hypotheses. The posterior probability is a central measure of uncertainty within the Bayesian approach and is used to quantify strength of evidence about hypotheses, such as the probability of superiority, which we used in our study. With available data, an external statistical group (Berry Consultants, College Station, TX, USA) undertook predictive power calculations of trial success or futility for the planned number of participants, to ascertain whether to stop or continue accrual. After the 315th index procedure, the statistical group communicated that accrual of patients was complete.

We did primary endpoint analyses 6 months after the last patient completed the index procedure. We defined success for the primary intent-to-treat efficacy analysis when the posterior probability of responding to treatment in the airway bypass arm (Pt) was superior to the posterior probability of responding to treatment for the sham control arm (Pc), with probability (Pr) of 96·5%. Trial success requires that $\pi > 0 \cdot 965$, where $\pi = Pr[Pt > Pc]$. Additional prespecified analyses included: sensitivity for participants lost to follow-up; effects of unmasking; complete 6-month data, excluding loss to follow-up; treatment and control and time-modelled data, with logistic regression; and secondary endpoints. For continuous variables, we calculated p values with the two-sample *t* test, whereas for binary variables we used Fisher's exact test. For the composite primary safety endpoint, we used Bayesian methods to compare rates of serious adverse events between the airway bypass and sham control arms, in specified time binds. Non-inferiority for the 6-month primary safety endpoint required that the posterior probability be greater than 0·95.

This study is registered with ClinicalTrials.gov, number NCT00391612.

Role of the funding source

Broncus Technologies funded the trial and was responsible for trial design and coordination and data analysis. The corresponding author and writing committee had full access to all data and had final responsibility for the decision to submit for publication.

Results

Between Oct 18, 2006, and April 8, 2009, 1522 people were screened for the study and 319 underwent randomisation. 212 participants were randomly assigned airway bypass (four were allocated after enrolment closed

so did not receive the intervention) and 107 were allocated sham control (figure 1). 6-month follow-up data were available for 195 (94%) patients in the airway bypass arm and 90 (84%) who were assigned sham control. Seven (3%) participants in the airway bypass arm and seven (7%) who were assigned sham control were lost to follow-up due to death or lung transplantation. Demographic and baseline characteristics were matched between groups (table 3).

	Airway bypass (n=208)	Sham control (n=107)
Day 1 to month 6		
≥1 exacerbation or infection	33 (15·9%)	9 (8·4%)
1 exacerbation or infection	27 (13·0%)	8 (7·5%)
2 exacerbations or infections	6 (2·9%)	1 (0·9%)
≥3 exacerbations or infections	0 (0%)	0 (0%)
Month 6–12		
≥1 exacerbation or infection	29 (13·9%)	12 (11·2%)
1 exacerbation or infection	23 (11·1%)	12 (11·2%)
2 exacerbations or infections	3 (1·4%)	0 (0%)
≥3 exacerbations or infections	3 (1·4%)	0 (0%)
Day 1 to month 12, cumulative		
≥1 exacerbation or infection	52 (25·0%)	18 (16·8%)
1 exacerbation or infection	36 (17·3%)	15 (14·0%)
2 exacerbations or infections	10 (4·8%)	2 (1·9%)
≥3 exacerbations or infections	6 (2·9%)	1 (0·9%)

Data are number (%). COPD=chronic obstructive pulmonary disease. *Events meeting the definition of a primary safety composite endpoint are excluded.

Table 6: **COPD exacerbation or infection, up to 12 months post procedure***

Mean (SD) procedure time (min) for airway bypass was higher than for sham control (107 [29] *vs* 60 [5]; p<0·001). In individuals allocated airway bypass, insertion of 1280 stents was attempted (mean [SD] passages, 6·2 [1·8] per patient, range 2–14) and 981 (76·6%) stents were placed in total (4·7 [1·4] per patient). Placement of stents was unsuccessful in three patients allocated to the airway bypass arm. For participants receiving three or more stents, no correlation was noted between RV reduction and increasing stent number (*r*=–0·05; figure 2). Small sample sizes limit interpretation for individuals with two stents or fewer.

In the pre-procedure period, 14 (7%) patients assigned airway bypass and eight (8%) allocated sham control had a respiratory-related serious adverse event, indicative of morbidity associated with emphysema. Despite 1280 attempted stent placements, serious adverse events arising 0–7 days post procedure were reported in seven (3·4%) participants in the airway bypass arm versus none in those allocated sham control. One periprocedural death

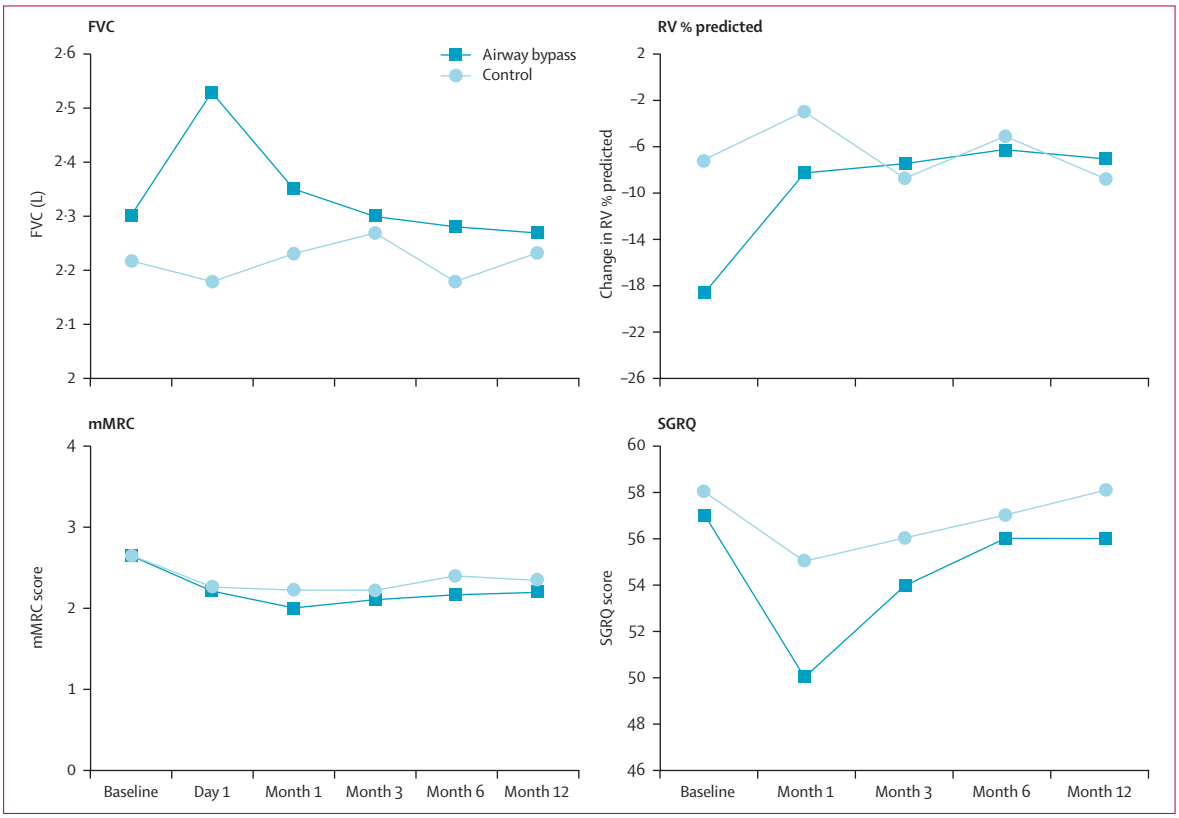

Figure 3: **Primary and secondary efficacy endpoints**
Data are mean values by follow-up visit. FVC=forced vital capacity. mMRC=modified Medical Research Council dyspnoea score. RV=residual volume. SGRQ=St George's respiratory questionnaire.

	Day 1	Month 1	Month 3	Month 6	Month 12
Co-primary efficacy endpoints					
FVC (L)					
Airway bypass	0·27 (0·6)	0·06 (0·4)	0·02 (0·4)	−0·03 (0·4)	−0·08 (0·5)
Control	0·00 (0·4)	0·02 (0·3)	0·04 (0·3)	−0·04 (0·4)	0·00 (0·4)
p value*	<0·001	0·329	0·551	0·870	0·208
mMRC (0–4)					
Airway bypass	−0·41 (0·9)	−0·63 (1·0)	−0·53 (0·9)	−0·47 (1·0)	−0·41 (1·0)
Control	−0·41 (0·8)	−0·43(0·9)	−0·42 (0·9)	−0·22 (0·9)	−0·25 (1·0)
p value*	0·960	0·085	0·357	0·045	0·212
Pulmonary function endpoints					
RV (L)					
Airway bypass	−0·38 (0·8)	−0·15 (0·6)	−0·12 (0·6)	−0·061 (0·7)	−0·06 (0·7)
Control	−0·12 (0·6)	0·01 (0·7)	−0·14 (0·6)	0·03 (0·5)	−0·10 (0·6)
p value*	0·017	0·083	0·803	0·705	0·718
RV (% predicted)					
Airway bypass	−17·9 (38)	−6·8 (29)	−6·0 (29)	−4·7 (31)	−5·6 (32)
Control	−5·8 (25)	−1·2 (31)	−7·5 (26)	−3·7 (25)	−7·4 (27)
p value*	0·016	0·121	0·654	0·781	0·677
FEV_1 (L)					
Airway bypass	0·09 (0·2)	0·02 (0·1)	0·01 (0·1)	−0·01 (0·1)	−0·02 (0·2)
Control	0·00 (0·1)	0·01 (0·1)	−0·01 (0·1)	−0·02 (0·1)	−0·04 (0·1)
p value*	<0·001	0·217	0·110	0·406	0·186
FEV_1 (% predicted)					
Airway bypass	3·1 (6)	0·7 (4)	0·3 (4)	−0·3 (4)	−0·15 (7)
Control	0·1 (3)	0·3 (3)	−0·2 (3)	−0·6 (3)	−1·1 (3)
p value*	<0·001	0·277	0·231	0·445	0·269

Data are mean (SD) change from baseline. FVC=forced vital capacity. mMRC=modified Medical Research Council dyspnoea scale. RV=residual volume. FEV_1=forced expiratory volume in 1 s. *From a two-sample *t* test.

Table 7: **Changes from baseline for co-primary efficacy and secondary endpoints**

	Baseline	Month 1	Month 3	Month 6	Month 12
6-min walk test (m)					
Airway bypass	302 (88)	314 (95)	310 (105)	295 (105)	281 (109)
Control	297 (85)	302 (90)	307 (85)	296 (90)	297 (94)
p value*	0·644	0·291	0·793	0·893	0·256
SGRQ (mean)					
Airway bypass	57 (13)	50 (15)	54 (16)	55 (17)	56 (16)
Control	58 (13)	55 (17)	56 (17)	57 (14)	58 (15)
p value*	0·349	0·006	0·303	0·448	0·339

Data are mean (SD). SGRQ=St George's respiratory questionnaire. *From a two-sample *t* test.

Table 8: **Functional outcomes over time**

arose related to a ruptured aortic aneurysm on day 1. One major haemoptysis in the airway bypass arm was controlled during bronchoscopy. Two patients developed pneumothorax requiring intercostal drainage for more than 7 days, and two developed COPD exacerbations and were admitted for longer than 7 days. One patient with respiratory failure was ventilated for more than 24 h.

30 (14·4%) participants assigned airway bypass had at least one composite safety endpoint compared with 12 (11·2%) allocated sham control (table 4). Most events were COPD exacerbations or pulmonary infections needing admission for longer than 7 days. Of individuals who had a composite safety endpoint event, four patients (three in the airway bypass arm and one assigned sham control) had more than one. Composite 6-month death rates were similar between the two groups, with most deaths due to respiratory causes. Overall, 12-month mortality was 6·7% in the airway bypass arm and 6·5% for sham control, with similar Kaplan-Meier curves.

Beyond composite events, rates of respiratory serious adverse events were higher for pneumothorax, haemoptysis, and COPD exacerbations in patients assigned airway bypass than in those allocated sham control (table 5). The raised overall COPD rate in the airway bypass arm is attributable to more participants having events and with one or more exacerbation. At 12 months, rates of COPD exacerbation and pulmonary infection were similar between treatment arms (table 6).

With respect to co-primary efficacy endpoint measures, mean FVC increased from baseline to day 1 in patients allocated airway bypass but returned to baseline values by month 3 (figure 3). Mean mMRC scores decreased from baseline to day 1 in both groups and remained lower than baseline up to 12 months.

Bayesian analysis therefore failed to show any superiority of airway bypass, with a posterior probability of 0·749, below the Bayesian success threshold of 0·965. Bayesian analysis also showed non-inferiority for the 6-month composite safety endpoint, with a posterior probability of 1·00, compared with the success threshold of greater than 0·95.

On day 1 post procedure, significant improvements in RV, RV/TLC, and FEV_1 were noted in patients assigned airway bypass compared with those in the sham control arm (table 7). However, the acute benefits in pulmonary function tests in the airway bypass arm declined by month 1. SGRQ total score was improved significantly with airway bypass compared with sham control, but only at month 1 (figure 3, table 8).

At baseline, homogeneity of CT-based lung volumes, as measured by percent point difference in density mask from lower to upper lobes, was similar for patients allocated sham control (right −5·4%; left −4·7%) and airway bypass (right −6·1%; left −5·2%). At day 1, total CT-based percent reductions in RV from baseline were significantly greater in the airway bypass arm (−6·8%) than in the sham control arm (−1·1%, p<0·001). Percent changes in RV per lobe were significantly greater with airway bypass compared with sham control for all lobes at day 1, but not at month 6 (figure 4).

To investigate potential explanations for the loss of treatment benefit at 6 months, CT analyses of stent patency and associated RV changes were completed for

133 of 208 patients assigned airway bypass who had clinically meaningful reductions in RV (more than –10% at day 1 from baseline). At day 1, 45% (60/133) of those with CT scans available had six stents identified, compared with only 25% (35/133) at 6 months, indicating loss of stents over time, presumably due to expectoration. Clinically, 24 (11·5%) participants reported stent expectoration, similar to the stent loss rate of 13% at 6 months measured by CT.

To gauge the effect of stent occlusion on late RV changes, 638 stent lumens were graded as either completely clear or containing tissue density at some level. On day 1, 66% (n=421) of stents were graded as completely clear, which fell to only 21% (n=124) by 6 months. Percent reduction in RV in lobes in which stents were graded as completely clear at 6 months was –8·4% (n=57), similar to the –10% (n=115) at day 1, indicating that reduction in RV is preserved if the stent is free from tissue density. CT analyses showed that stent placement conferred lobe-based RV reductions that were not maintained at 6 months, with return-to-baseline RV values in association with tissue density within the stent.

By month 6, 12 reports had been made of accidental unmasking of team A, with eight attributable to patient-reported stent expectoration. Unmasking happened in 24 (11·5%) patients after expectoration of a stent. A Bayesian analysis to assess the effect of unmasking showed that the posterior probability that the unmasked airway bypass outcome was superior to masked airway bypass outcomes was 0·339, whereas the probability that unmasked sham control outcomes was inferior to masked sham control outcome was 0·41. Neither probability exceeded the 0·95 level needed to suggest that unmasking altered findings of the EASE trial.

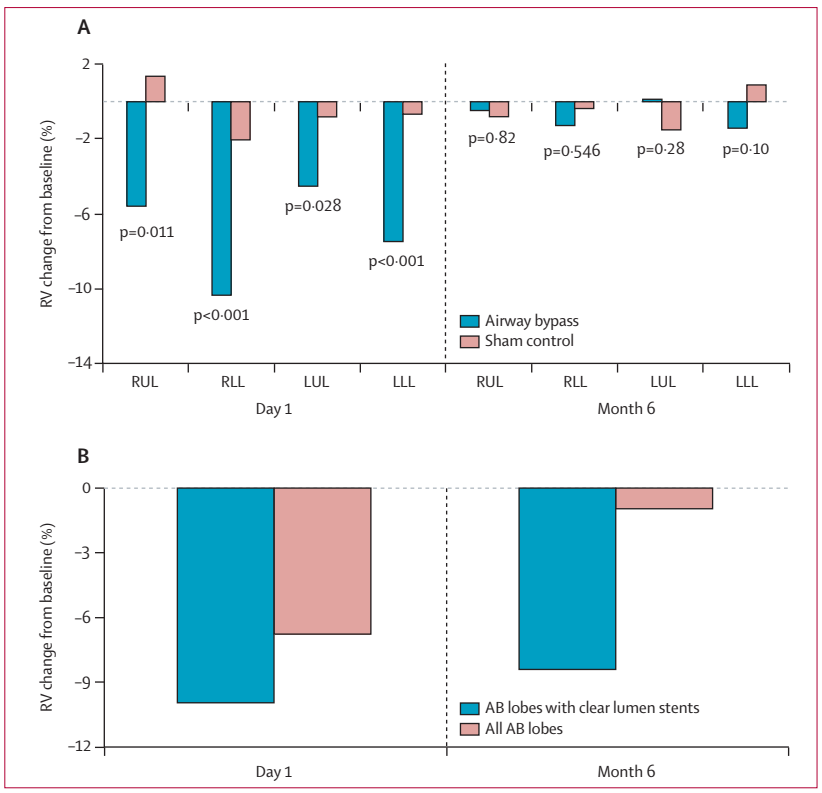

Figure 4: **CT-based lobar RV changes**
(A) RV changes by lobe. (B) RV changes in AB lobes with at least one clear visible stent. RUL=right upper lobe. RLL=right lower lobe. LUL=left upper lobe. LLL=left lower lobe. RV=residual volume. AB=airway bypass.

Discussion

Findings of the EASE trial showed that at day 1, airway bypass released trapped gas from hyperinflated regions, thereby improving pulmonary function. However, durability was limited by pulmonary function tests and subjective, functional, and post-hoc CT measures. Outcomes for sham control and airway bypass were similar at months 3, 6, and 12. Although the EASE trial failed to show a difference between treatment arms with respect to the 6-month primary efficacy endpoint, invaluable lessons were learned (panel 2).

The high morbidity and mortality rate reported for lung-volume reduction surgery underlies the quest for bronchoscopic alternatives. In the National Emphysema Treatment Trial,[1] the death rate (when the high-risk group was excluded) was 5·2% within 90 days of the index procedure, compared with 0·5% for airway bypass and 1·9% for sham control in the EASE trial over the same timescale. Mortality in the Endobronchial Valve for Emphysema Palliation Trial[15] was 2·8% at 6 months, similar to findings of the EASE trial (1·9% for airway bypass and 3·7% for sham control). Despite very severe COPD, participants in our study tolerated the airway bypass procedure and anaesthesia, with a 7-day composite safety rate of only 3·4%. EASE procedural safety data show that this very unwell population can tolerate general anaesthesia and a complex bronchoscopy procedure. During the first year, individuals assigned to airway bypass had both more respiratory serious adverse events and more events per patient compared with sham control. However, follow-up reports of respiratory serious adverse events were about 21% in year 2 for the airway bypass arm, similar to levels seen with sham control in year 1.

Procedural variability could have restricted the initial reduction in lung volume achieved. Participants assigned to airway bypass underwent between two and 14 passages and received up to six stents (0–3 stents per lobe). Wide variation in RV reduction was noted (+8 to –29%) between lobes. Unique to the EASE trial, RV reductions were seen in lower and upper lobes, indicating that bronchoscopic reduction can be achieved in homogeneous disease. Stents were not always placed at the passage site because of friable mucosa, difficult stent access, delivery, or doppler evidence of blood flow. Improvements are needed for identification of and navigation to desired target areas and definition of procedural success.

Panel 2: Research in context

Systematic review

We searched for all studies (up to the year 2011) on bronchoscopic lung-volume reduction to identify case reports, series, and clinical trials in which airway bypass was used. Previous studies showed that use of stents for airway bypass was technically feasible and seemed to be safe. A feasibility study in 35 patients showed reduction in the amount of hyperinflation, with corresponding improvement in pulmonary function and dyspnoea. We identified no previous randomised controlled trial that assessed safety or efficacy of the Exhale stent in the airway bypass procedure.

Interpretation

This double-blind randomised study of airway bypass for end-stage emphysema failed to show durable benefit by pulmonary function tests or functional measures. Its relevance to the clinical community lies in detailed and time-dependent data gathered to establish the natural history and lessons for future interventions. Complex bronchoscopic procedures can be completed in this high-risk population with an acceptable safety profile. Release of trapped gas provides transient relief to patients with severe emphysema when drugs, nutritional support, rehabilitation, and supplementary oxygen only have limited effect.

The main limitation of the airway bypass procedure was the short duration of the initial benefit. All primary and secondary measures, including regional assessments by CT, returned to baseline by 6 months, except mMRC. Loss of the initial benefit is probably attributable to a combination of factors: passages that were created but not stented, which contributed to initial release of trapped air but which then closed within 7–14 days; stents that were expectorated; and loss of stent patency between day 1 and month 6. Factors that might have contributed to stent occlusion are mucus, granulation tissue, and collateral ventilation, with insufficient pressure gradient to maintain airflow.[7] The most probable cause of stent occlusion at day 1 is mucus collection. In a few patients who underwent repeat bronchoscopy after 6 months, stents were occluded by thickened mucus filling the proximal end of the stent or by a tissue layer formed across the distal end of the stent. Either way, the paclitaxel-silicone polymer dose-release combination was inadequate at maintaining stent patency.

The co-primary efficacy endpoint based on dual response to FVC (12%) and mMRC (1 point) posed a very high threshold for clinical success and masks the ability to interpret effects on pulmonary function and quality of life independently. The mMRC was developed to assess level of disability suffered by emphysema patients, using a limited subjective scale for changes in dyspnoea.[16]

Variation in selection, definition, and endpoints used for surgical and bronchoscopic emphysema trials makes comparison of findings difficult.[17] Ideal endpoints would be clinically relevant, objective, continuous variables that could guide individual responses and interventional field development. Uniform reporting of procedural success and inclusion of further interval follow-up are needed to define and optimise the treatment response and advance the area.

Despite the acute reduction in regional air trapping with an acceptable safety profile, the EASE trial failed to showed sustained long-term effects in patients with severe homogeneous emphysema. The future use of airway bypass will require improvement of durability to preserve RV reduction.

Contributors

PLS, D-JS, PFGC, EC, KV, BL, and GWS recruited and treated patients in this trial. All authors helped to write the report. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

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Conflicts of interest

The sponsor of the study (Broncus) reimbursed all clinical trial expenses incurred by the study centres. MER is chief medical officer and sits on the board of directors for Broncus. JDC is a consultant for Broncus. All other authors declare that they have no conflicts of interest.

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